Best Practice

EVIDENCE-BASED CASE REVIEW

Osteoma cutis (cutaneous ossification)

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Objectives

- Understand the possible systemic significance of cutaneous calcification and ossification
- Learn the clinical classification of osteoma cutis and calcinosis cutis
- Understand the diagnostic work-up
- Recognize the treatment options

Cutaneous calcification and ossification both involve the deposition of calcium salts in cutaneous and subcutaneous tissues. Derangements of calcium metabolism can sometimes cause cutaneous calcification or ossification as a first sign of systemic disease. Both processes (referred to in the dermatology literature as calcinosis cutis and osteoma cutis) are rare, with only scattered cases reported in the literature. Cutaneous calcification (calcinosis cutis) is traditionally divided into four broad categories: metastatic, dystrophic, iatrogenic, and idiopathic (Table 1).[1]

Metastatic cutaneous calcification is calcium deposition due to a disorder of calcium or phosphorus homeostasis and is usually associated with elevated serum calcium or phosphate levels. Dystrophic calcification is calcification that develops as part of a preexisting pathologic skin process such as a tumor. This form of cutaneous calcification shows no elevations of serum calcium or phosphate values. Cutaneous ossification (osteoma cutis) is likewise divided into categories, referred to as primary and secondary osteoma cutis.

Osteoma cutis

I. Primary
- a) Albright's hereditary osteodystrophy
- b) Not associated with Albright's hereditary osteodystrophy
  - i) Multiple miliary osteomas of the face
  - ii) Isolated osteoma
  - iii) Widespread osteoma
  - iv) Congenital plaque-like osteoma

II. Secondary
- a) Inflammatory skin disease
  - i) Progressive systemic sclerosis and CREST syndrome
  - ii) Dermatomyositis
  - iii) Morphea
- b) Tumors/Neoplasms
  - i) Basal cell carcinoma, pilomatricoma, etc.
- c) Trauma and scars

Secondary osteomas account for 85% of cutaneous ossifications and develop within preexisting neoplastic or inflammatory skin lesions. Primary osteoma cutis accounts for about 15% of cutaneous ossifications and develops on its own (see box above).[2]

Information on the topics discussed in this review and following case history was obtained through a literature search using PubMed and the following key words: cutaneous ossification,[1,3] osteoma cutis,[2,4,5] and calcinosis.[6] A 4-mm punch biopsy was fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin. Sections were examined using light microscopy. Clinical data were obtained through direct interview with the patient as well as review of laboratory and radiograph records.

Case history

A 66-year-old African-American woman with a history of coronary artery disease, congestive heart failure, diabetes, and hypertension presented with incidental findings of multiple firm, nontender, subcutaneous plaques and nodules involving the lateral aspect of the right and left thighs, extending to the knees (Figure 1). The nodules had been present for 30 years, recently increasing in number after a myocardial infarction. At times she had also suffered from painful extrusions of "chalky bone." The patient denied any history of trauma, inflammatory changes, nevi, or other dermatologic conditions. She had no other significant medical conditions and no family history of similar skin lesions.

Laboratory studies showed an elevated erythrocyte sedimentation rate of 114 mm/hour, a random glucose of 157 mg/dl, a mildly depressed total serum iron and iron saturation (27 ug/dl and 10%, respectively), and mildly elevated blood urea and nitrogen (28 mg/dl) and creatinine (1.6 mg/dl). The rest of the laboratory results, including electrolytes, serum calcium, phosphate, alkaline phosphatase, and angiotensin-converting enzyme levels, were within normal limits.

Her chest X ray showed a prominent right hilum with calcified lymph nodes. Venous Doppler examination of lower extremities, to rule out deep venous thrombosis, was technically difficult because of severe calcium deposits. A 4-mm punch biopsy obtained from the right leg showed variably sized spicules of mature lamellar bone within the subcutaneous fat (Figure 2).

Table 1 *Some causes of dermatologic calcifications*[7]

Dystrophic	Metastatic	Idiopathic	Iatrogenic
Progressive systemic sclerosis	Chronic renal failure	Subepidermal calcified nodules	I.V. calcium chloride/ gluconate therapy
CREST syndrome	Sarcoidosis	Idiopathic calcification of the scrotum	
Panniculitis	Albright's hereditary osteodystrophy	Tumoral calcinosis	
Ehlers-Danlos	Neoplasms	Progressive osseous heteroplasia	
Cutaneous neoplasm	Pseudohyper-parathyroidism		
Trauma			
Infection			

What medical conditions are associated with cutaneous ossification and cutaneous calcification?

Cutaneous ossification (osteoma cutis) can be divided into primary and secondary osteoma cutis, both of which are quite rare. Primary osteoma cutis is divided into two subclasses. The first is associated with Albright's hereditary osteodystrophy, which has poor long-term prognosis. Two syndromes are included in Albright's hereditary osteodystrophy: pseudohypoparathyroidism and pseudopseudohypoparathyroidism. The characteristic features of both syndromes include obesity, developmental disability, short stature, round facies, basal ganglia calcification, and osteoma cutis.[2,3] Patients with pseudohypoparathyroidism have end-organ resistance to the action of parathyroid hormone and have hypocalcemica/hyperphosphatemia, despite high levels of parathyroid hormone. Patients who have pseudopseudohypoparathyroidism are similar phenotypically except that the results of their laboratory tests are within normal limits.

Patients with the subclass of primary osteoma cutis that is not associated with Albright's hereditary osteodystrophy have a good long-term prognosis. The subclass is further divided: multiple miliary osteoma of the face, isolated osteoma, widespread osteoma, and congenital plaque-like osteoma.[3] Multiple miliary osteoma is restricted to the face and usually occurs in women. Isolated osteoma can occur at any cutaneous site and presents as a single isolated nodule. Widespread osteoma presents in the neonatal period as multiple generalized subcutaneous osteomas. Likewise, congenital plaque-like osteoma occurs in the neonatal period but morphologically presents as a large plaque on the extremities or the scalp.

Secondary osteoma cutis is quite rare, but relatively more common than the primary form, accounting for 85% of all cutaneous ossifications. By definition, secondary osteoma cutis occurs in association with antecedent skin inflammation, injury, or tumor[4] (box). Some of the clinically significant lesions include neoplasms (metastatic bronchogenic carcinoma, basal cell carcinoma, Gardner's syndrome, hemangioma), inflammatory skin disease (syphilis, pyogenic granuloma, folliculitis), and collagen vascular disease (CREST syndrome, dermatomyositis, lupus erythematosus).[4] Hence a thorough diagnostic work-up is important, because cutaneous ossification is not just a sign of present systemic disease, it may even precede it.

Cutaneous calcification (calcinosis cutis) and osteoma cutis overlap in terms of their pathogenesis and associated conditions (Table 1). Dystrophic calcification, the most common form of calcinosis cutis, does not alter patients' levels of serum calcium or phosphorus, but it shares many of the same underlying conditions with secondary osteoma cutis. Dystrophic calcinosis cutis can result from neoplasms, granulomatous conditions, collagen vascular disease (in particular CREST syndrome), systemic lupus erythematosus, and childhood dermatomyositis.

On the other hand, metastatic calcification is that form of calcification that results from increased serum calcium or phosphate levels. Multi-organ involvement of kidney, lungs, and arteries is common, but at times metastatic calcification can present as calcinosis cutis. Cutaneous lesions are most commonly seen in patients with chronic renal failure and are thought to be due to poor phosphate clearance. In this clinical setting, nodules of calcinosis cutis have a periarticular distribution and usually resolve when patients' levels of serum calcium and phosphorus return to normal. Metastatic cal-

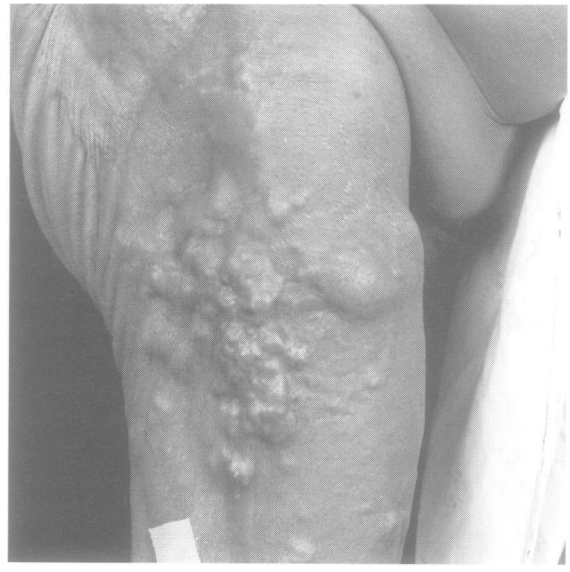

Figure 1 *Bilateral multiple hard subcutaneous nodules and plaques are present on the lateral thighs of this 66-year-old woman.*

cinosis cutis has also been reported in association with AIDS, lymphomas, pseudohyperparathyroidism, and sarcoidosis.

What is the diagnostic approach?

This case is somewhat difficult to classify. The extent of ossification in this patient prompted us to look for a systemic disease, particularly one that might alter calcium and phosphorus homeostasis, but the patient's levels of serum calcium and phosphate were normal. The fact that the patient developed the lesions near the age of 35 years ruled out many of the congenital and neonatal primary cutaneous ossifications. The patient also did not have phenotypic features of Albright's hereditary osteodystrophy or the hypocalcemia/hyperphosphatemia associated with pseudohypoparathyroidism. The absence of a secondary process within the biopsy ruled out secondary cutaneous ossification, as occurs in tumors, nevi, or other inflammatory conditions, and the patient had no clinical signs to suggest a collagen vascular disorder, such as progressive systemic sclerosis. Also in the differential diagnosis was cutaneous calcification and its associated conditions (Table 1), ruled out by a combination of history, laboratory data, and, most importantly, biopsy appearances. Histopathologically, calcinosis cutis demonstrates masses of basophilic material, usually surrounded by a chronic granulomatous foreign body-type inflammatory reaction. In contrast, osteoma cutis demonstrates either basophilic or eosinophilic deposits arranged in the form of spicules. In contrast to calcinosis cutis, osteoma cutis demonstrates the characteristic lamellar arrangement of mature bone when viewed via polarization microscopy.

A rare form of secondary cutaneous ossification occurs in association with chronic venous insufficiency and preferentially affects the lower extremities; in most patients, however, the cutaneous osteomas are localized to the lower leg, not the upper leg, as in this patient.[7] Furthermore, this patient had no obvious clinical symptoms or signs of venous insufficiency.

In summary, this patient presents an unusual form of cutaneous ossification restricted to the bilateral thighs. Because there is no apparent associated dermatologic condition, we consider it a form of idiopathic non-Albright's hereditary osteodystrophy primary osteoma cutis, which aside from its cosmetic deformity is of no serious clinical consequence.

What are possible pathogenic mechanisms for osteoma cutis?

The mechanism of cutaneous ossification is unclear, but most theoretical speculations suggest that the bone deposition is due to the ability of either resident fibroblasts or nests of pleuripotent mesenchymal cells to differentiate into osteoblasts.[5]

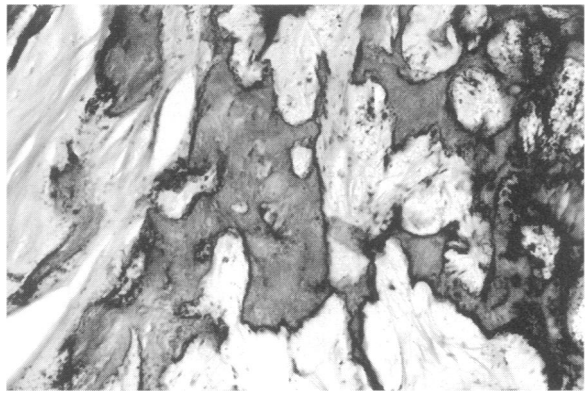

Figure 2 *Within the deep dermis and subcutaneous fat are multiple spicules of mature lamellar bone.*

What are the treatment possibilities?

The treatment of underlying disease is the first step. Various medical and surgical therapies have been tried for individual lesions of osteoma cutis. Unfortunately, synthetic diphosphonates, such as etidronate disodium, do not seem to be effective in treatment. Surgical excision, including punch excisions, are currently the treatment of choice for osteoma cutis, if the patient is symptomatic. Ultrasound studies may aid in surgical planning by localizing small and deeper lesions.[8]

Like osteoma cutis, the treatment of calcinosis cutis has met with varied success.[4] In general, diphosphonates and steroids have also not been successful. Diltiazem treatment has been reported to cause dramatic calcinosis regression in systemic scleroderma. There have been similar reports of success with diltiazem use in juvenile dermatomyositis.[6] One theory behind the action of diltiazem is that it prevents calcium influx into the calcifying tissue and that this is followed by macrophage clearance of the lesion.[4] Surgical treatment is also an option for cutaneous calcification, particularly in cases of physical impairment, recurrent ulcerations, unremitting painful lesions, or cosmetic deformity.

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